RET Gene Analysis in Hirschsprung disease

Disorder also known as: HSCR; Congenital aganglionic megacolon

Clinical Features:
Hirschsprung disease is the main genetic cause of functional intestinal obstruction in infants and children, with an incidence of 1 in 5000 births. It is associated with congenital absence of parasympathetic ganglia in the bowel. The majority of patients with HSCR (80%) have a short aganglionic segment (S-HSCR) affecting the region beneath the upper sigmoid. Patients with long-segment HSCR (L-HSCR), representing 20% of cases, have aganglionosis extending to or beyond the splenic flexure. HSCR presents as an isolated finding in ~70% of patients, while ~30% of cases are considered syndromic (associated with either a chromosome abnormality or multiple congenital anomalies). RET is the primary gene underlying HSCR, particularly in families with multiple cases of L-HSCR; however, evidence shows that the phenotype can result from pathogenic variants in several other genes with both recessive and dominant inheritance patterns (acting alone or in combination). Notably, RET variants show incomplete, sex-dependent penetrance and do not always result in the Hirschsprung phenotype.\(^1,2\)

Genetics:
Autosomal dominant with reduced penetrance.

Test Methods:
Analysis is performed by bi-directional sequencing of the nine exons of the RET gene in which HSCR-associated variants are most commonly identified (exons 2, 3, 5, 6, 9, 10, 12, 13, and 17). If no variant is identified, sequencing of the remainder of the RET gene can be performed upon request. Additionally, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion or duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, qPCR, or another appropriate method.

Test Sensitivity:
The sequencing approach used by GeneDx is expected to identify >99% of existing variants in RET gene. Constitutional variants in the coding region of the RET gene have been found in up to 50% of familial and 10-35% of non-familial (isolated) HSCR. Patients with L-HSCR are more likely than patients with S-HSCR to have an identifiable RET variant. 76% of RET variants that have been reported in association with HSCR are located in the nine select exons listed above, and the remaining variants would be expected to be identified by sequencing of the rest of gene.\(^1,2\) Rarely, deletions of the entire RET gene, which would not be identifiable by
sequencing but would be detected by ExonArrayDx analysis, have also been reported in association with Hirschsprung disease.\textsuperscript{3,4} Additionally, partial deletions of the RET gene have been observed at GeneDx.

**References:**